Subverting misconceptions about radiation therapy

To the Editor:

More than a century after the discovery of ionizing radiation, its pleomorphic effects on living organisms continue to puzzle and inspire investigations on how to optimize this powerful therapeutic tool. The recent publication by Price *et al.* investigates the effect of whole-body irradiation on radiation-resistant Langerhans cells (LCs) and their migration to lymph nodes to elicit the generation of regulatory T cells (T_{reg} cells)[1]. The authors ascribe the radiation resistance of LCs to heightened activation of the cyclin-dependent kinase inhibitor CDKN1A (p21), a stalwart mechanism of protection from radiation in many normal and malignant cells. Cell-cycle arrest mediated by p21 extends the opportunity for a cell to execute the DNA-damage response and repair and thereby avoid deletion by apoptosis.

The mechanism described builds on pre-existing evidence of diminished immunosurveillance of irradiated normal skin[2] and introduces an immunological dimension to the role of radiation as a carcinogen[3]. The authors speculate that the peculiar resistance of LCs to radiation and their induction of T_{reg} cells might have evolved as a mechanism to preclude autoimmunity toward the skin, an organ constantly exposed to damage from ultraviolet radiation. Interestingly, among atomic-bomb survivors exposed to total-body radiation, the excess relative risk of skin cancer was 15, 5.7 or 1.3 as a function of age with exposure at an age of 0–9, 10–19 or 20–39 years, respectively[4]. This age-dependent effect is intriguing from an immunological point of view, since an opposite trend would be expected on the basis of diminishing immunocompetence with age.

However, the generalization of these findings to clinical radiotherapy is invalid.

Experimental mice received total-body irradiation (TBI) in large doses (6 or 12 Gy, near and exceeding, respectively, the dose lethal to 50% of C57BL/6 mice) before being challenged by subcutaneous injections of B16 melanoma tumor cells. Irradiated mice developed larger tumors than their unirradiated control counterparts did shortly after TBI treatment (within 12–24 h), but the effect was abolished when mice were inoculated 5 weeks after TBI.

As Price *et al.* acknowledge in the discussion of their findings[1], the use of TBI in these experiments has little in common with the usual clinical practice of radiotherapy, in which localized radiation is delivered to established tumors, in a highly targeted fashion, with much effort expended to avoid normal tissue through the strategic use of fractions of much lower dose administered over time. Extensive experience in treating skin cancer with single-modality radiotherapy has demonstrated lasting tumor control in approximately 90% of basal cell carcinomas and 80% of squamous cell carcinomas[5]. Radiation therapy has maintained its solid role in the therapeutic arsenal for the treatment skin cancer since the 1900s[6], a fact difficult to reconcile with the conclusions of Price *et al.*[1]. Unfortunately, misinterpretation of this paper as evidence for a general immunosuppressive action of radiotherapy is already being delivered to the public (http://medicalxpress.com/news/2015-09-doctors-caution-radiotherapy-skin-cancer.html).

Thus, the work of Price *et al.*[1] needs to be considered in the context of current research delineating how localized radiotherapy of cancer can have both pro-immunogenic effects and immunosuppressive effects. The identification of critical cross-talk between radiation-induced signals and the immune system of cancer carriers offers the opportunity to both optimize the clinical use of radiotherapy and enhance the effects of cancer immunotherapies[7]. This rationale has inspired ongoing therapeutic investigations that combine immunotherapy agents to correct the immunosuppressive effects of radiation and/or enhance its immune system–promoting effects. For example, clinical radiotherapy can be successfully combined with blockade of immunological checkpoints that counteracts a radiation-induced increase in T_{reg} cells[8]. Moreover, evidence is emerging that local radiation therapy can convert a tumor into an individualized cancer vaccine in a setting of otherwise ineffective immunotherapy and can work in concert with immunotherapy to control the primary tumor and metastasis outside the radiation field[9,10].

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Price, Idoyaga and Merad reply:

A recent article from our group reported on an underlying mechanism of resistance to depletion by ionizing irradiation that is used by LCs, a unique population of dendritic cells that reside in the epidermis[1]. Formenti *et al.* raise one major objection to our report: that our mouse model system bears little resemblance to clinical radiotherapy. In our tumor-challenge experiments, we administered TBI at a dose of 6 Gy to mice that we subsequently challenged subcutaneously with B16 cells. As stated in our initial report, our goal was two-fold. First, we sought to determine the effect of conditioning-radiation therapy on the local

immunological milieu, independently of any direct tumoricidal effect of radiation itself on an established tumor. Second, we sought to further characterize the mechanisms by which tumors evade local control following radiation therapy. To that end, we were able to identify a novel mechanism by which radioresistant LCs promote tumor-protective T_{reg} cells following radiation exposure.

Formenti *et al.* assert that this model bears little resemblance to the practices of clinical radiation oncology; we certainly concede that TBI delivered at this dosage would not be used outside the setting of conditioning for bone marrow transplantation. We would argue, however, that our report might help inform ongoing research inquiries into the role of stereotactic radiosurgery (SRS) in combination radiation-immunological cancer therapies[2]. In SRS, high doses of radiation (for example, those exceeding 12 Gy) can be administered as a single dose with meticulous dose conformity that almost completely restricts ablative doses of radiation to the tumor and tumor bed while minimizing exposure to the skin. Therefore, and in line with the assertions of Formenti *et al.*, we can see that such SRS techniques take full advantage of all the technological progress brought to the radiation-oncology field in the past 20 years. Whereas our model focuses on the cutaneous response to TBI, we see definite utility in studying the immunological response of other tissues to ablative doses of radiation. As alluded to by Formenti *et al.*, the ability of radiation to 'unmask' tumor antigens following treatment permits synergy with blockade of immunological checkpoints to trigger abscopal (off-target) effects, in which distant tumors that did not receive radiation treatment actually regress in response to an effective radiation-induced immune response. By studying the effects of ablative doses of radiation on normal tissues, clinicians and researchers might in the future be able to guide SRS treatment to those tumors residing in tissues less permissive to the population expansion of T_{reg} cells following radiation and thereby promote more-potent abscopal effects.

In addition, our initial report demonstrates that when the population expansion of T_{reg} cells is blocked by the radio-sensitization of LCs through selective deletion of CDKN1A (p21), tumor growth is concomitantly diminished. This finding is in line with other studies demonstrating the power of T_{reg} cells in abolishing the beneficial effects of radiotherapy[3]. It is also consistent both with clinical discussions highlighting the role of T_{reg} cells following radiation therapy[4] and preclinical models in which T_{reg} cells increase in number following radiation and in which their subsequent depletion enhances the response to radiation therapy administered either as TBI or as targeted therapy[5]. Similarly, and of certain clinical relevance, the use of inhibitors of immunological checkpoints can inhibit the polarization to T_{reg} cells in the setting of cancer[6]. While we did not specifically analyze this intervention in our report, it is definitely a viable target for intervention to preempt the deleterious population expansion of T_{reg} cells following radiotherapy.

Ultimately, as highlighted in this journal[7], we do not seek to undermine current radiotherapy treatment paradigms at all, a result Formenti *et al.* duly fear misinterpretation of our data might cause. Conversely, we seek to emphasize the paramount importance of synergistically combining radiotherapy with immunotherapy. To this end, several groups, including that of Formenti *et al.*, have done critical proof-of-principle research demonstrating the ability of radiation to enable systemic tumor control in conjunction with immunological adjuvants such as GM-CSF[8] or inhibitors of immunological checkpoints such as ipilimumab[9]. However, other research has described the ability of radiation to act in synergy with immunotherapies to enhance the diversity of the T cell antigen receptor repertoire of tumor-infiltrating lymphocytes[10].

Looking ahead, several ongoing phase I/II clinical trials (such as NCT01497808) are explicitly analyzing the potential of combining SRS with the blockade of immunological checkpoints. Moreover, several other potential lines of inquiry have been opened on how to best integrate radiation and immunological therapies. Open questions about optimal fractionation schedules, treatment timing and radiation dose, in addition to determining which adjuvant systemic therapies best complement radiation therapy, all promise rich frontiers in the field[11]. In the end, our goals and those of Formenti *et al.* are one and the same: by fully harnessing the treatment modalities in the oncologist's armamentarium, whether radiation therapy, chemotherapy or surgery, with immunological therapies such as checkpoint blockade and immunological adjuvants, we hope to aid future practitioners to effect potent, safe and durable local and systemic control of cancer for the benefit of their patients.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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